
ASHI
ASHI 51ST ANNUAL
MEETING
#ASHI2025
OCTOBER 6TH- 10TH, 2025
HYATT REGENCY GRAND CYPRESS
ORLANDO, FLORIDA

CONFLICT OF INTEREST

Nick Borcherding
Assistant Professor
Washington University, St Louis, MO, USA

I have financial relationship(s) with:

Consultant
Columbus Instruments

Stockholder
Epana Bio

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Previous Employment
Santa Ana Bio
Omniscope

Predicting TCR Specificity in the Age of Single-Cell Sequencing

Nick Borcherding, MD, PhD

2025/10/06

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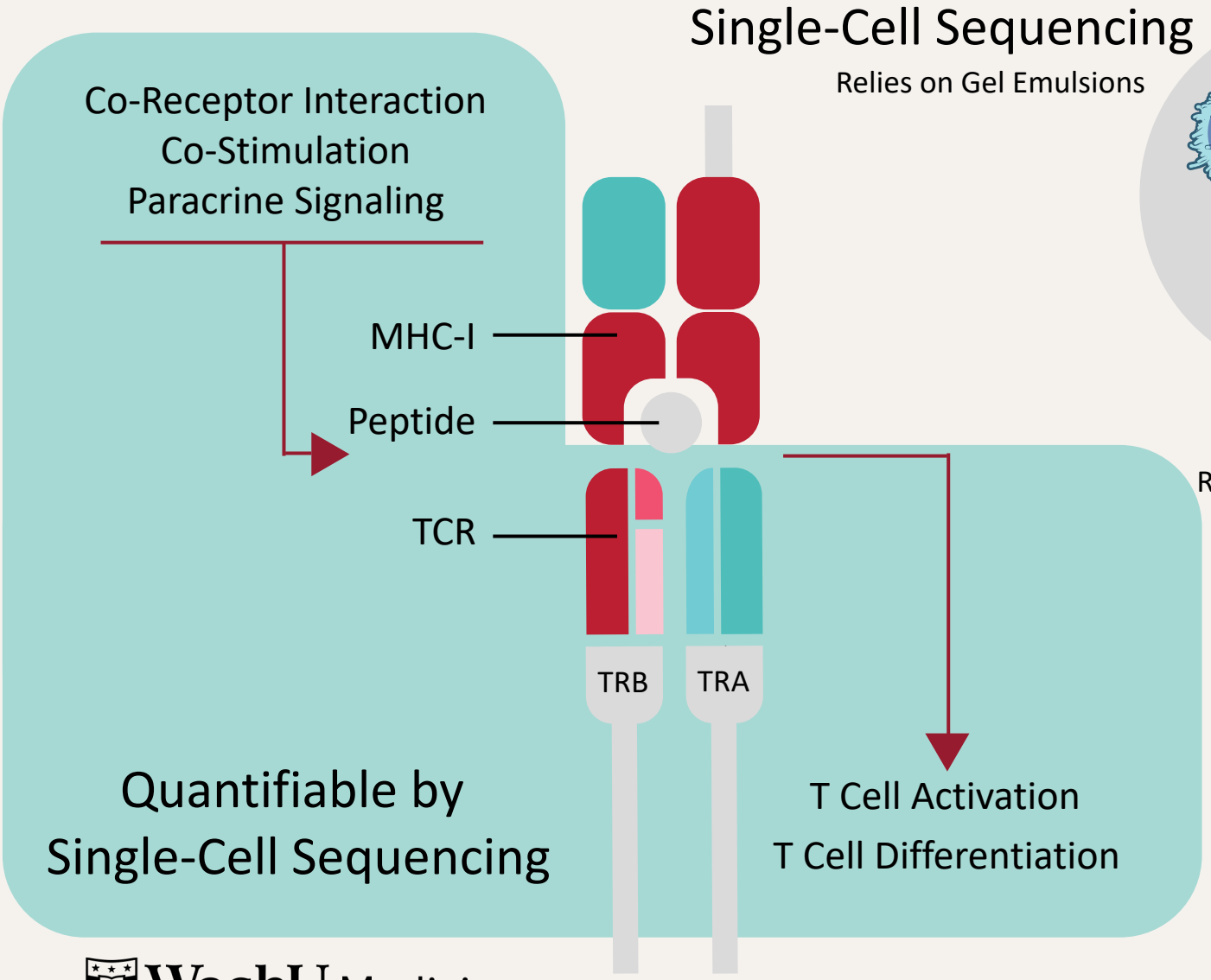
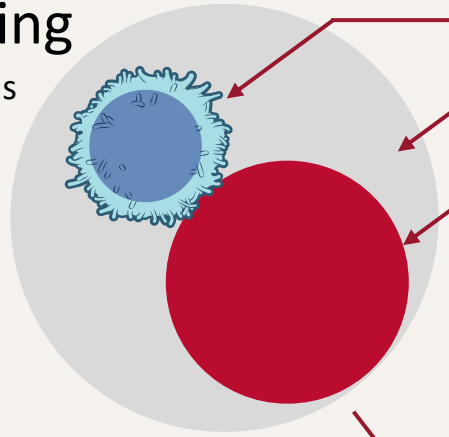
Examining the T cell response with single-cell sequencing

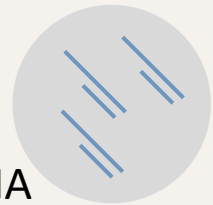


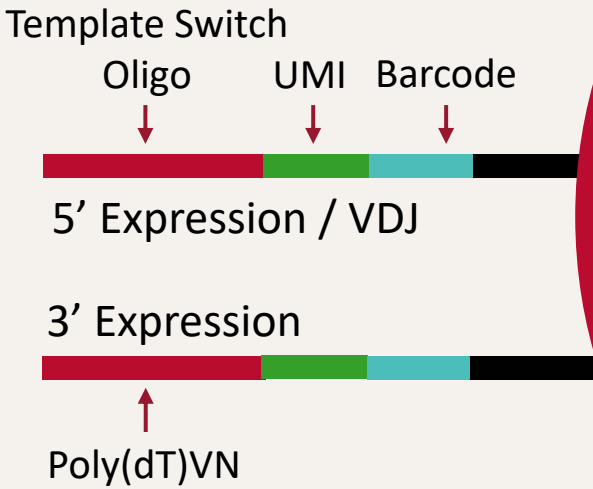
Single-Cell Sequencing

Relies on Gel Emulsions



Cell Lysis
Reverse Transcription





Single-Cell Quantification
of Gene Expression and TCR

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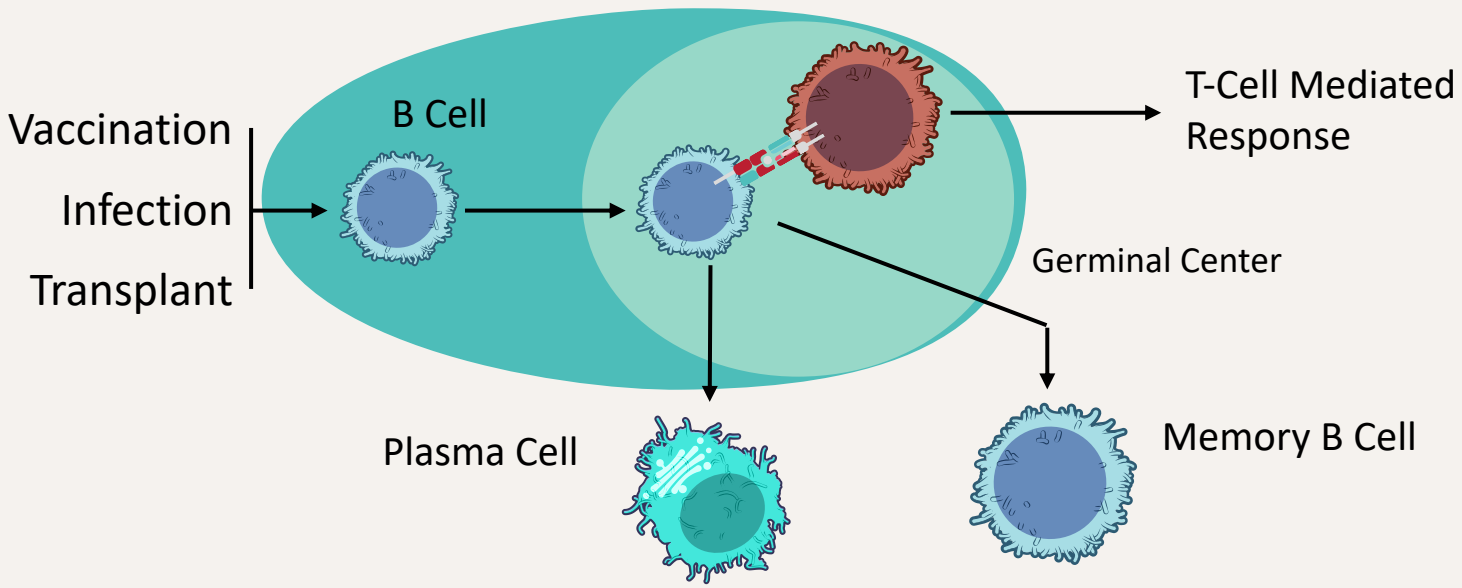
Examining T_{FH} Responses in mRNA Vaccination

Central Node in Vaccine Response

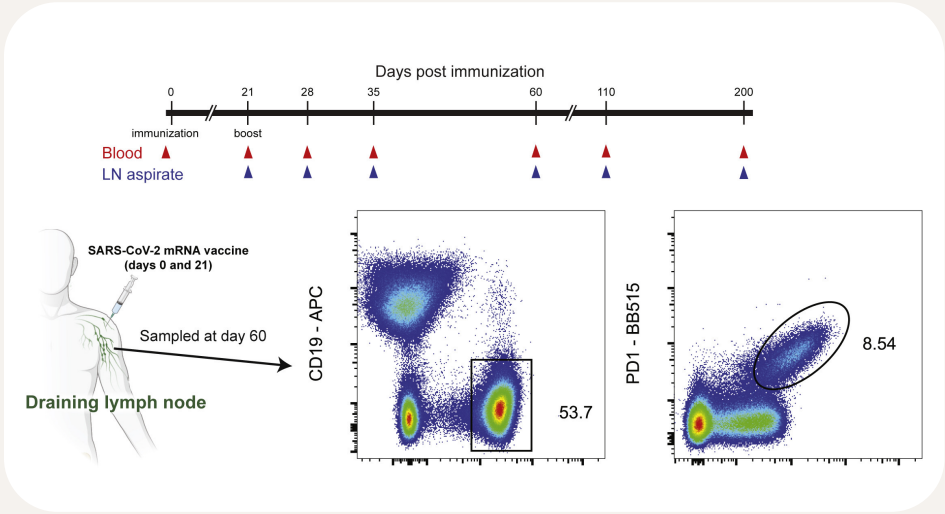
T Follicular Helper (T_{FH}) → Antigen Specific



Philip Mudd

Ali Ellebedy

COVID19 Vaccination Cohort 0-200 Days



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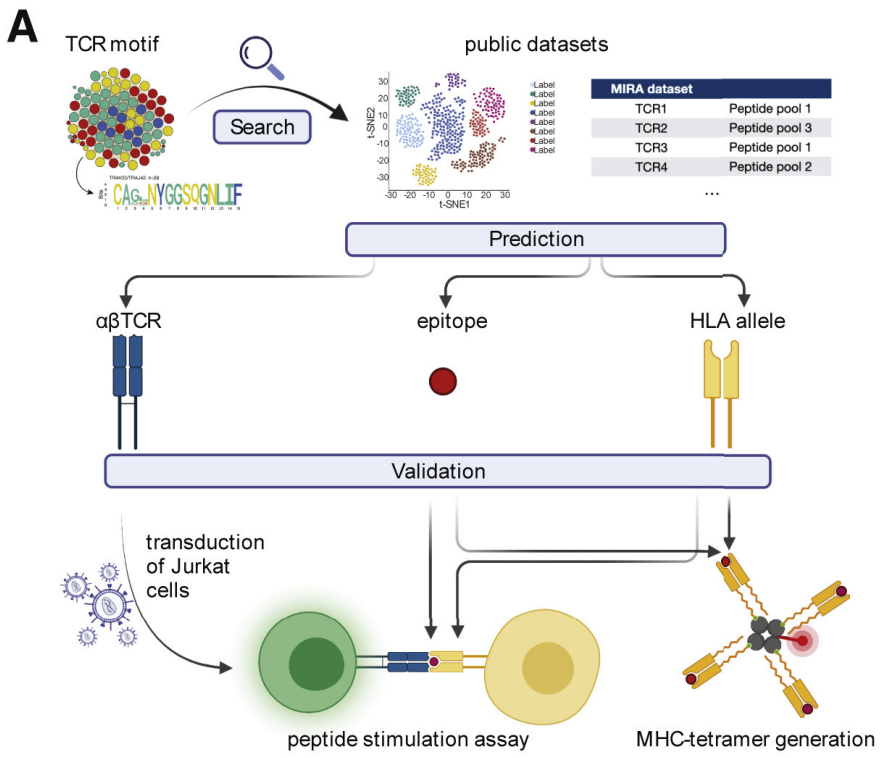
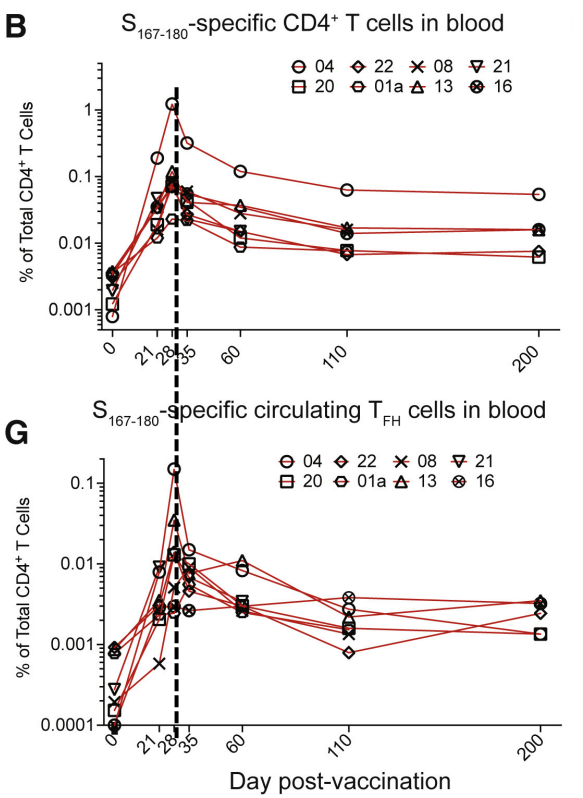
Mapping Antigen-Specific Responses





Revisit the validation in the coming slides

HLA-DPB1*04-restricted Subjects

Epitope: Spike$_{167\text{-}180}$
TCR-A Chain Driven
Peaks at 28 Days (7 Days post-Boost)

Perfect for a Computational Immunologist

1. Restricted/Timed Antigen Exposure
2. Shared HLA
3. Tetramer-sorted TCR Sequences
4. Unanalyzed Single-Cell Cohort

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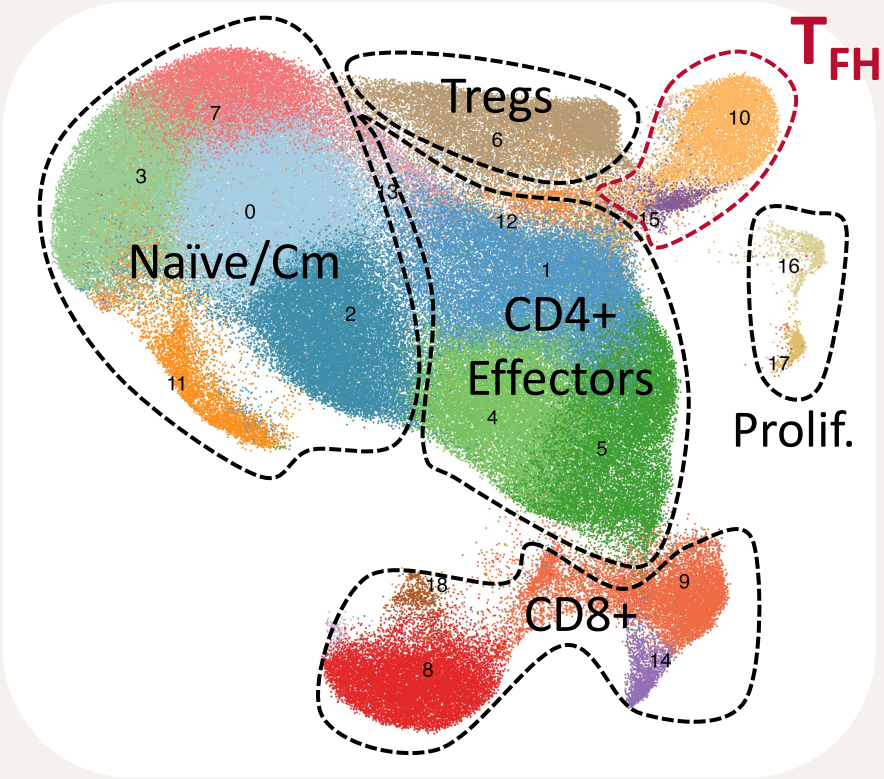
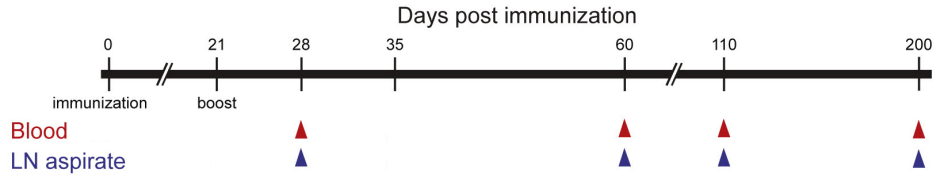
T-cell Landscape of COVID-19 Vaccination in Lymph Node and Blood

HLA-DPB1*04-restricted
T Cell COVID scRNA Vaccination Atlas

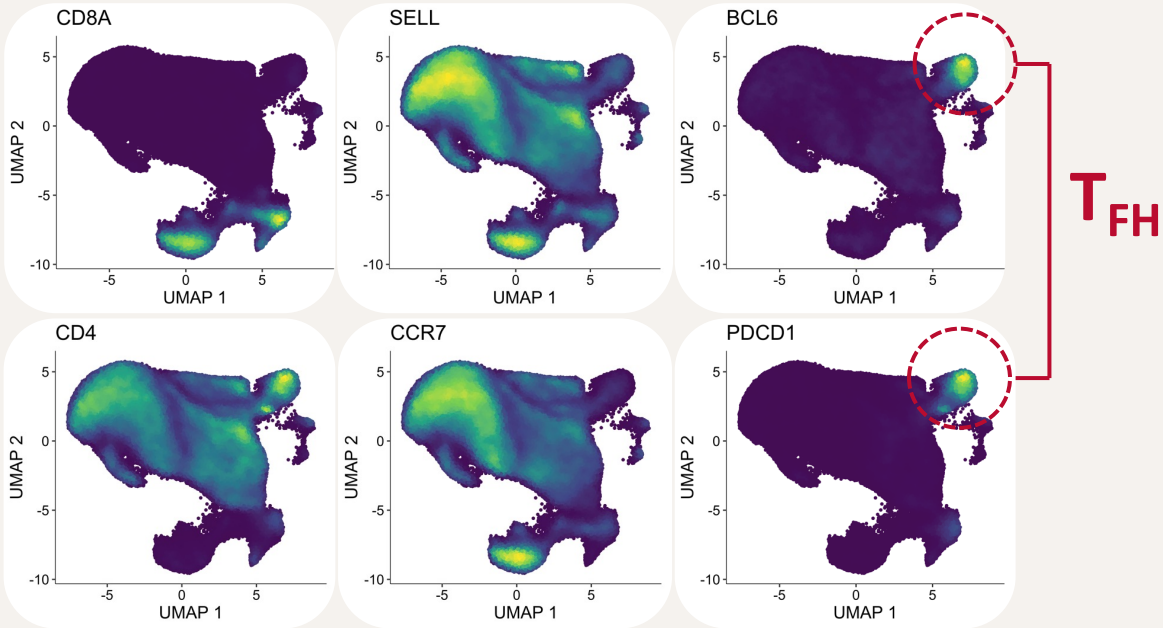


N = 219,284

Sample with Single-Cell Sequencing Results



Refine Cell Type Annotation Via Gene Expression



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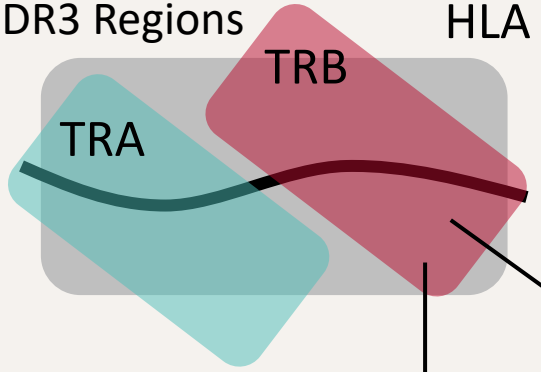
Inferring Antigen Specificity using TCR Sequences

CDR3 Regions

HLA



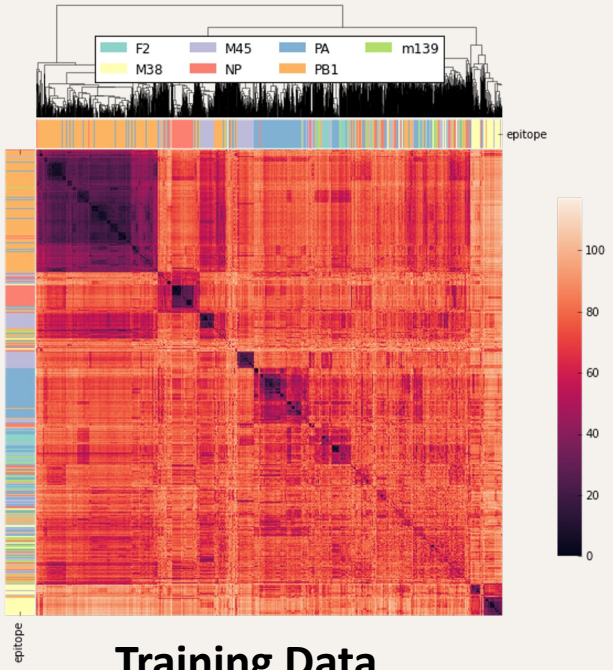
Peptide

C A S S Q

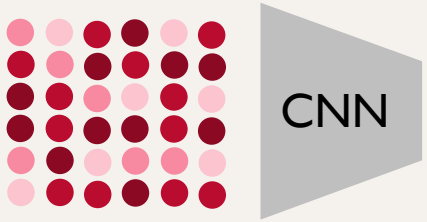
C A S G Q

TRB CDR3 Sequence

Sequence Similarity → Antigen Specificity



C A S G Q



CNN

Latent Dimensions

Amino Acid Characteristics

Training Data

TCRB: 1,276,462

TCRA: 905,611

C A S S Q

CDR3 Sequence

1.0 0.3 3.2 2.0 0.8

Numerical Vector

https://github.com/BorchLab/Trex

Trex (**TCR** and **Ex**pression)

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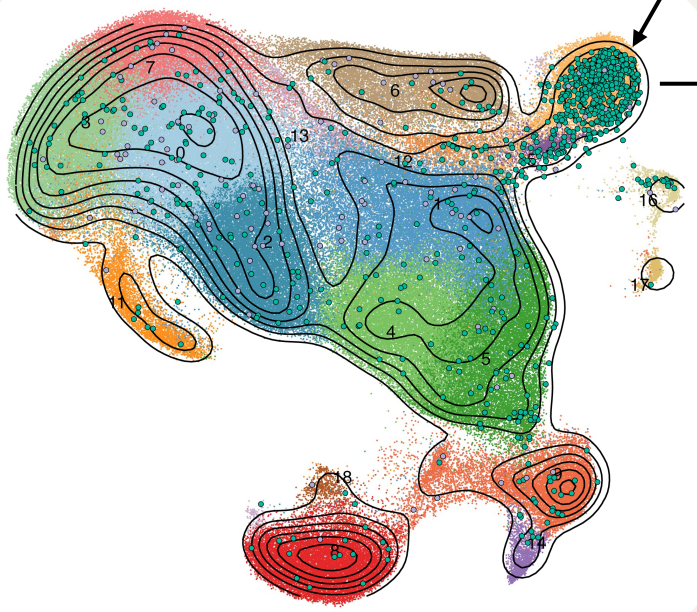
Applying Trex to T_{FH} Response in Vaccination

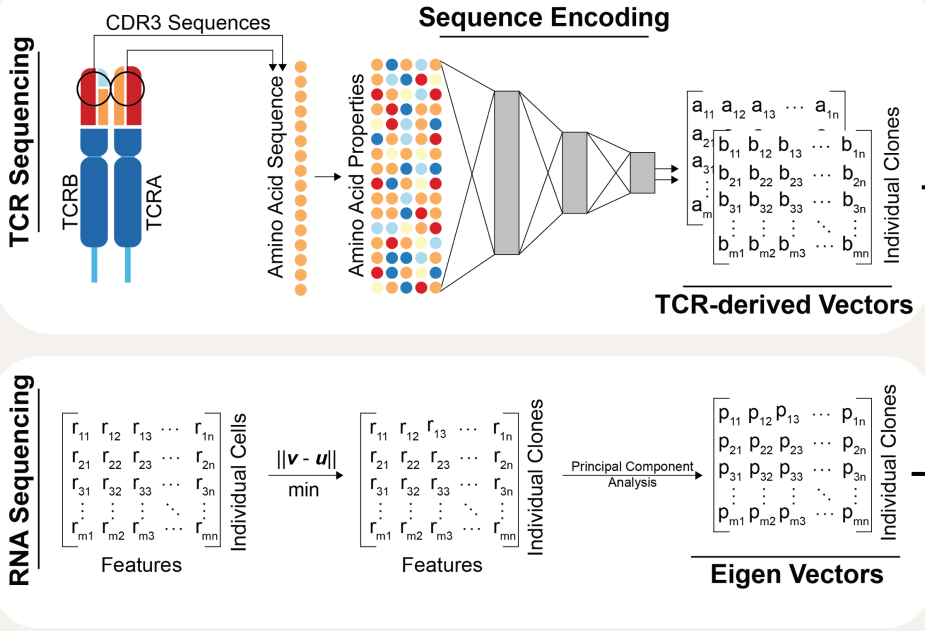
T_{FH} Cells

Previously Validated with Tetramers



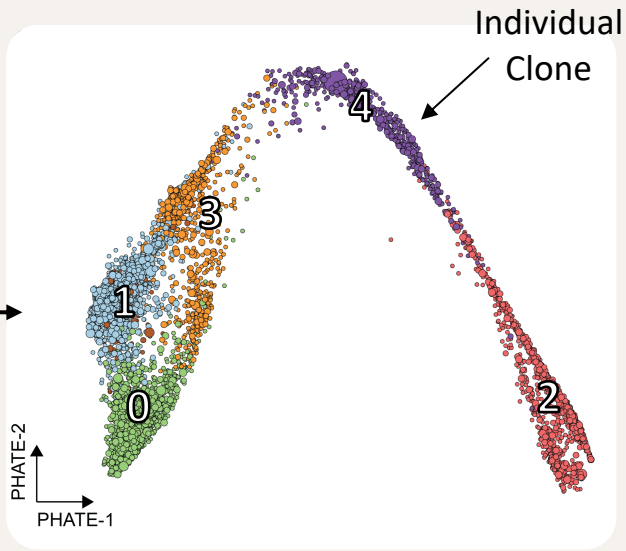
- $Spike_{167\text{-}180}$ TCR
- Other Spike TCR

Applying **Trex** to TRA and TRB Sequences



PCA Values Based on RNA

T_{FH} Response
RNA + TCR



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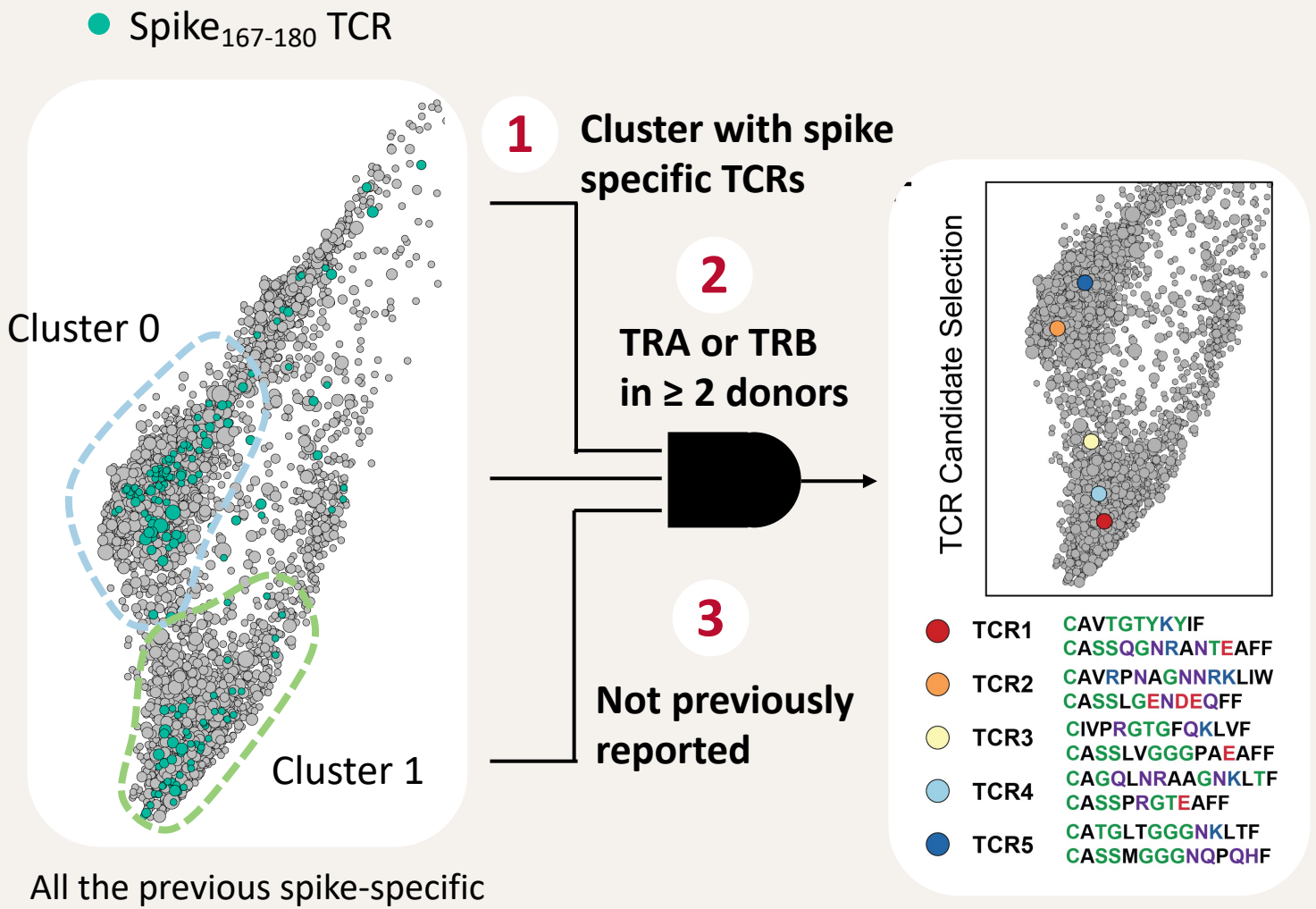
Inferring Spike-Specific TCRs



All the previous spike-specific clones localized to 2 clusters

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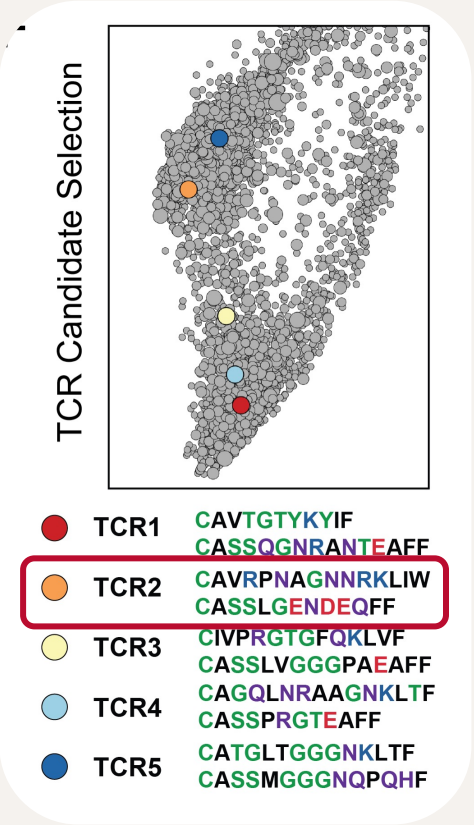
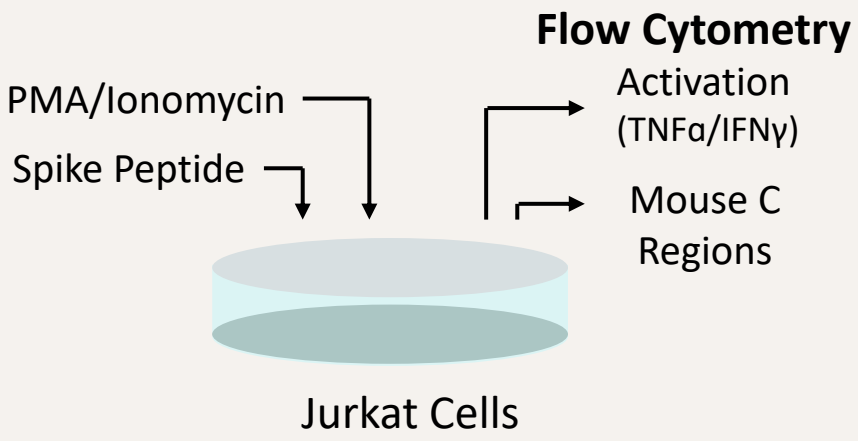
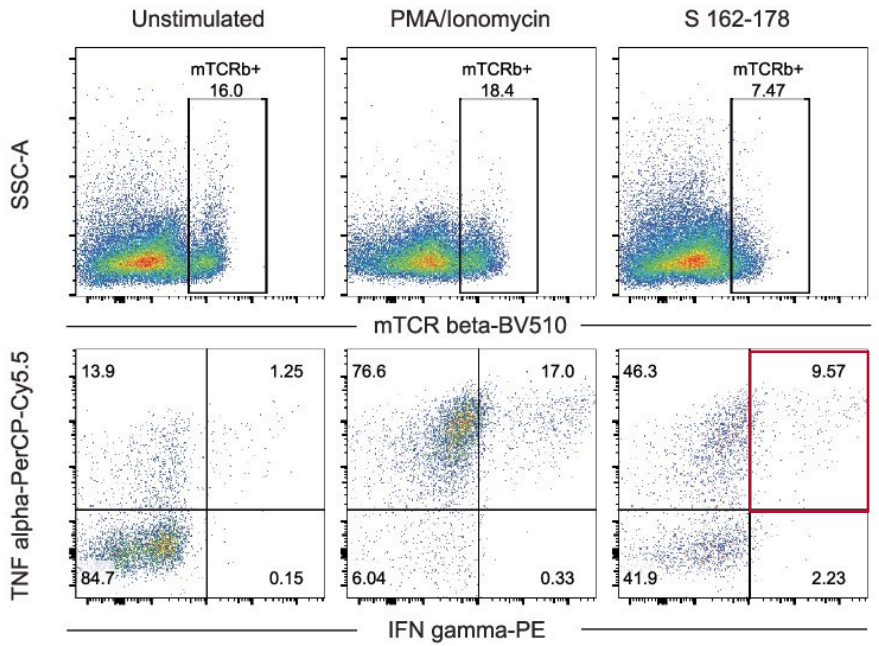
Mapping TCR Candidates to Antigen and HLA



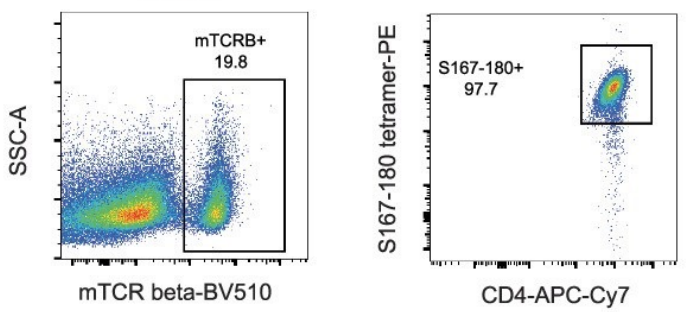
AIM – Activation Induced Marker



Spike Epitope	HLA
TCR1: S575-591	?
TCR2: S167-180	DPB1*04:01
TCR3: S869-878	DRB5*02:02
TCR4: S204-213	DRB1*07:01
TCR5: S120-136	DPB1*02:01



Tetramer Sorting



Incredibly Labor Intensive and Expensive Process

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Lessons from Predicting TCR Specificity from Trex

Positives

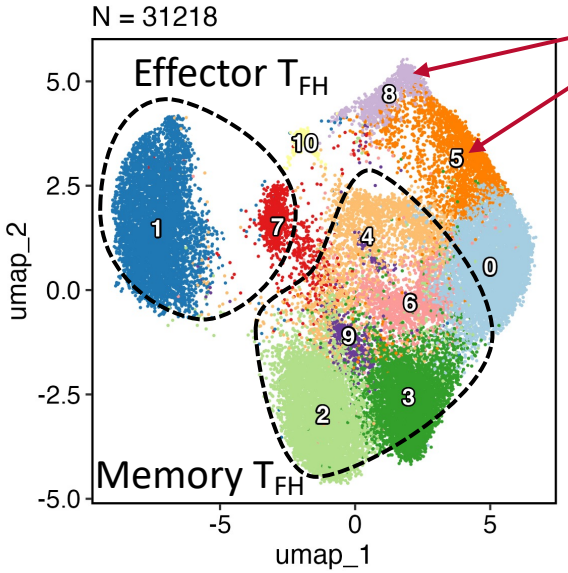
- Inferring TCR antigen specificity is possible
- **5 of 5 Candidate TCRs** were spike-specific

Negatives

- **TCR + Expression approach is not sufficient**:
  - Epitope Specificity
  - HLA Restriction
- Requires substantial prior knowledge

Next Chapter in of T_{FH} response to mRNA vaccinations

Lymph node samples from patients received vaccination boost



Novel T_{FH} Clones/Response

Protein Language Models

Edit Distance-Based Network Analysis

TCRA/TCRB ± HLA

TCRA/TCRB ± HLA

The combination appears to improve predictions

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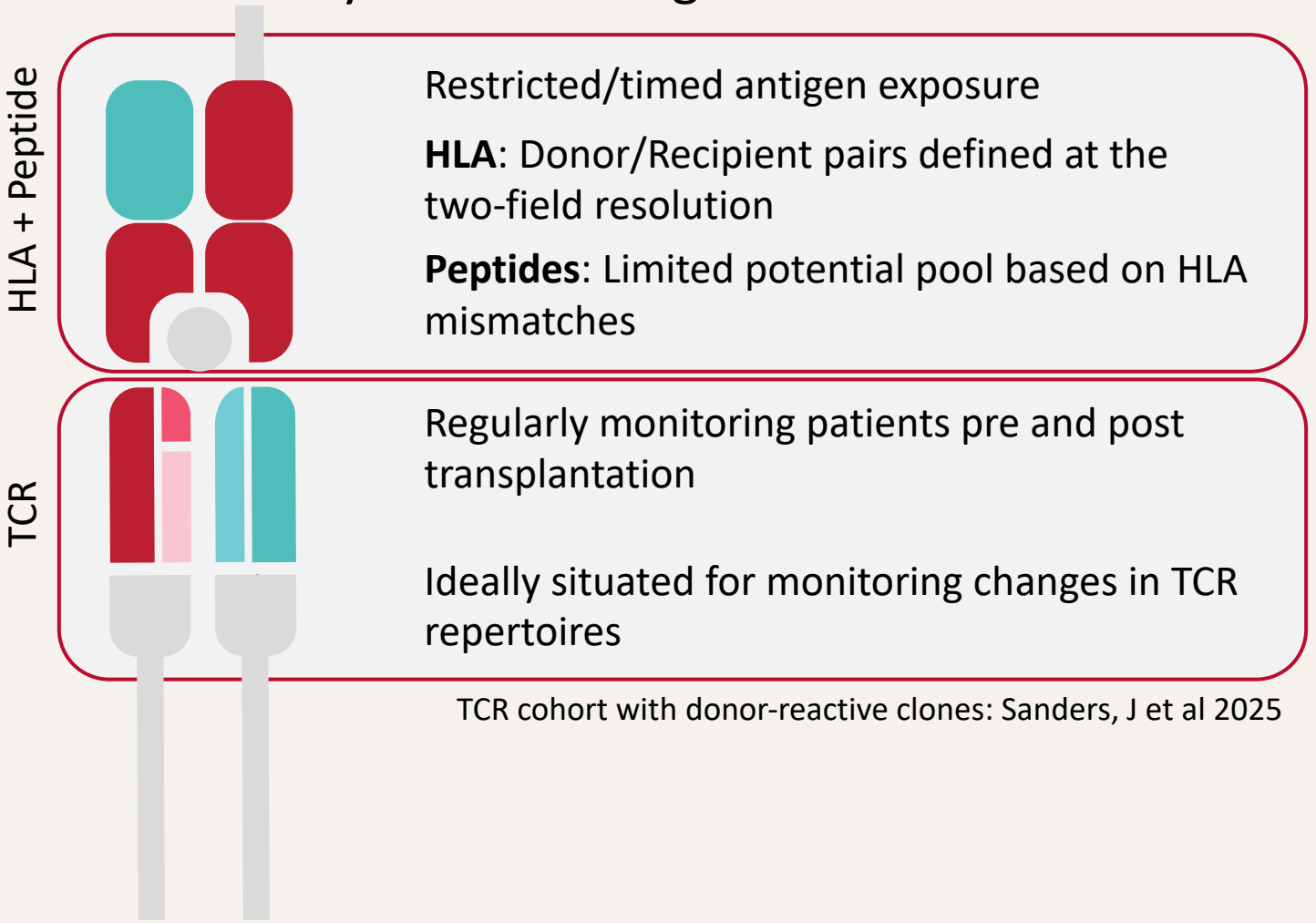
Translating TCR Antigen Prediction to Organ Transplant

Ideal Fixed System for Antigen Prediction



Restricted/timed antigen exposure

HLA: Donor/Recipient pairs defined at the two-field resolution

Peptides: Limited potential pool based on HLA mismatches

Regularly monitoring patients pre and post transplantation

Ideally situated for monitoring changes in TCR repertoires

TCR cohort with donor-reactive clones: Sanders, J et al 2025

Obstacles

Predicting Immunodominant Allopeptides

Antigen Binding Models Are Not Trained On
1) Self/Allo-peptides
2) Neoantigens (Tumor-associated)

Deep Paired TCRA/B Sequencing

New techniques like TIRTL-seq from St. Judes

Pogorelyy, M 2024 Preprint

Computational Needs

Data scale
Negative data
Methods for unifying data across sources and methods

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